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EXAMINER	
VOGEL, NANCY TREPTOW	
ART UNIT	PAPER NUMBER
1636	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/526,525	SZPIRER ET AL.	
	Examiner	Art Unit	
	NANCY VOGEL	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *13-21 and 26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 22-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/19/07, 6/29/07, 6/29/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-26 are pending in the case.

Receipt of the Information Disclosure Statements on 9/19/07, 6/29/07, and 6/29/06 is acknowledged.

Applicant's election without traverse of Group III, claims 1-12 and 22-25, drawn to prokaryotic cells, CcdB/CcdA and Kis/Kid, in the reply filed on 1/21/09 is acknowledged.

Claims 13-18 and 26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 1/21/09.

Claim Objections

Claims 6 and by dependence claim 7 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The term "poison/antidote" does not further limit the term "toxic" and "antidote".

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-3, 5, 6, 7, 12, 22, are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims can read on a product of nature, untouched by the "hand of man", since the claims could be interpreted to read on a cell comprising chromosomal material ("genetic construct") in which genes encoding toxic molecules and antidote proteins are present in unmodified form.

Claim Rejections - 35 USC § 112

Claims 1-6, 8-12, 22-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is directed to a genetic construct and a cell comprising a genetic construct comprising a nucleotide sequence encoding a toxic gene and a genetic sequence encoding an antidote (or anti-toxic) molecule. At issue for the purpose of written description requirements is the lack of adequate written description for the claimed genus of "toxic genes/poison proteins" and the claimed genus of "antidote or anti-toxic genes".

Vas-cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written

description' inquiry, whatever is now claimed." (See page 1117.) The specification should "clearly allow persons of ordinary skill in the art to recognize that (he or she) invented what is claimed." (See Vas-cath at page 1116).

The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see In re Shokal 113USPQ283(CCPA1957); Purdue Pharma L.P. vs Faulding Inc. 56USPQ2nd 1481 (CAFC 2000).

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure.

With respect to the toxic genes and anti-toxic genes, the specification does not define the term "toxic gene", and thus the claimed genetic construct encoding toxic genes reasonably embraces an enormous genus of structurally distinct and undisclosed molecules. Furthermore, the claimed invention requires a nucleic acid encoding an "antidote gene" so as to suppress the enormous genus of structurally distinct and undisclosed toxic molecules. Rather, the specification discloses that the toxic genes/anti-toxic genes are, respectively: CcdB/CcdA, Kid/Kis, Doc/Phd, RelE/RelB, PasA/PasB/PasC, MazE/MazF and Hok/SoK,. However, the terms “toxic molecule” “poison”, “antidote” molecule can encompass any molecule which has a toxic effect on any cell or which molecule which can overcome the toxic effect. Therefore the genus encompassed is very large. Without a correlation between structure and function, the

claims do little more than define the claimed invention by function. That is not sufficient to satisfy the written description requirement. See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406 ("definition by function ... does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is").

The Revised Interim Guidelines state:

"The claimed invention as a whole may not be adequately described if the claims require an essential or critical element which is not adequately described in the specification and which is not conventional in the art" (col. 3, page 71434), "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus", "in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one
species within the genus" (col. 2, page 71436).

An Applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

Possession may also be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics

sufficient to show that the Applicant was in possession of the claimed invention. See, e.g., Pfaffv. Wells Elecs., Inc., 525 U.S. 55, 68, 1 19 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998), Regents of the University of California v. Eli Lilly, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997)*, Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it").

Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. See Fiers v. Revel, 25 USPQ2d 1602 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Based on the Applicant's specification, the skilled artisan cannot envision the detailed chemical structure of the nucleotide sequences which encode toxic and antidote genes as contemplated in the specification. Accordingly, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that the Applicant is in possession of the broad genus of "toxic genes/poison proteins", "antidote or anti-toxic genes". Thus, for the reasons outlined above, it is concluded that the claims do not meet the requirements for written description under 35 U.S.C. 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

Claims 1-6, 8-12, 22-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention. If not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731,737, 8 USPQ2ds 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification. Therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention. And thus, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The Breadth of the Claims and The Nature of the Invention

The claims are broad for encompassing genetic constructs which encode any toxin/antidote molecules functional in any animal, fungal, plant or prokaryotic cells.

The claims are broad for encompassing an enormous genus of structurally distinct and undisclosed molecules toxic to a given cell type, and an at least equally enormous genus of structurally distinct and undisclosed anti-toxin genes not known in the art at the time of filing, wherein the genetic sequence encoding the toxin and anti-toxin genes are described only by the function of the respective gene products. The claims are broad for encompassing said toxins and antidote molecule which are in a fusion protein, including unique cloning sites.

When analyzed in light of the specification, the nature of the invention is the use of poison/antidote genetic systems, commonly used in prokaryotic host cell systems to facilitate cloning, in eukaryotic host cells, e.g. yeast cells, plant cells, animal cells.

The Existence of Working Examples and The Amount of Direction Provided by the Inventor

With respect to the toxic genes and anti-toxic genes, the specification discloses that the toxic genes/anti-toxic genes are, respectively: CcdB/CcdA, Kid/Kis, Doc/Phd, RelE/RelB, PasA/PasB/PasC, MazE/MazF, ParE, ParD and Hok/SoK, . The specification does not provide working examples of the invention. The specification does not disclose any nucleotide sequences encoding fusion proteins active as toxic molecule or as an antidote to a toxic molecule, comprising several unique cloning sites

and a nucleotide sequence encoding a molecule toxic to a cell or an antidote to said toxic molecule.

The State of the Prior Art, The Level of One of Ordinary Skill and The Level of Predictability in the Art

The art has disclosed the toxin/antidote systems listed in claim 7, which are functional in bacterial host cells. However, the art has not disclosed systems other than these, nor has it disclosed predictable methods for discovering new toxin/antidote encoding genes in other organisms.

The Quantity of Any Necessary Experimentation to Make or Use the Invention

The instant specification fails to disclose genetically modified eukaryotic host cells possessing mutations or genes which confer resistance to the toxic activity of two different bacterial toxic molecules. The instant specification fails to disclose toxin/antidote encoding genes other than those recognized in the art and listed in claim 7. The specification fails to disclose protein fusions encoded by toxin/antidote encoding genes which have several unique cloning sites. Thus, due to the lack of sufficient guidance provided by the specification regarding to the issues set forth above, the unpredictability of the protein engineering art, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

Accordingly, the instant claims are rejected for failing to comply with the enablement requirement.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-12, 22-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and by dependence claims 2-12, 22-25 are vague and indefinite in the recitation of "A genetic construct which is suitable for an insertion/deletion or an inversion for at least one target nucleotide sequence" since it is not clear what is intended to be encompassed by this phrase. It is not clear in what sense the genetic construct is "suitable for an insertion/deletion or an inversion". It is not clear what the metes and bounds of the claimed subject matter are since it cannot be determined how the preamble limits the claimed subject matter. Claim 1 and by dependence claims 2-12, 22-25, is additionally vague and indefinite since it is not clear whether the recited first toxin and the recited antidote to a second toxic molecule encoding nucleotide sequences are intended to be both downstream of the promoter/activator sequence or only the first toxin encoding nucleic acid encoding molecule. Furthermore, it is unclear whether it is intended that the recited promoter/activator sequence is operatively linked, i.e. controls the transcription of, the recited first toxic molecule encoding nucleotide

sequence and/or the nucleotide sequence encoding the antidote to a second toxic molecule.

The term "unique" in claim 4 is a relative term which renders the claim indefinite. The term "unique" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear whether it is intended that the recited unique restriction sites are unique to the genetic construct, or the cell into which the genetic construct may be inserted, or the cell in which the genetic construct is present, etc.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 5-12, 23 are rejected under 35 U.S.C. 102(e) as being anticipated by Gabant et al.. (WO 02 066657).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome

either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Gabant et al. disclose a nucleic acid construct comprising a nucleic acid sequence (2) made of a nucleic acid sequence 3, encoding an antidote protein 4 (CcdA protein) to a toxic molecule (5) (CcdB protein) and a gene of interest (6), and a promoter/operator sequence (9); said cassette sequence (2) being disposed between a first and second recombination site (7) (8), which do not recombine with each other. Said nucleic acid construct (1) is integrated into a further vector which is an insert donor DNA vector (10) comprising a further selectable marker (11) (Kid protein). The insert donor DNA vector 10 could be amplified in a bacteria which is resistant to the activity of the first selectable marker 11 (kid protein), for instance , a bacteria expressing the antidote protein kis to the protein poison kid. This means that the endogenous kid promoter must be active in said bacteria. An origin and antibiotic resistance marker is present (14). The wording of claim 1: "A genetic construct comprised of a promoter/activator sequence (kid promoter in the reference) disposed upstream of a first nucleotide sequence encoding a first toxic molecule (Kid protein in the reference) and a second nucleotide sequence encoding an antidote to a second toxic molecule (CcdA protein in the reference) different from said first toxic molecule", is disclosed in Fig. 1.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NANCY VOGEL whose telephone number is (571)272-0780. The examiner can normally be reached on 7:00 - 3:30, Monday - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571) 272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/NANCY VOGEL/
Primary Examiner, Art Unit 1636

NV3/29/09